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09/607,142	06/29/00	CHERRY J	5443.424-US

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/607,142	Cherry et al.
Examiner	**Art Unit**
Christian L. Fronda	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above, claim(s) 1-4 and 6-9 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 5 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 09/386,607.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1 and 2, drawn to a method for preparing a maltogenic amylase variant comprising subjecting a DNA sequence encoding a maltogenic amylase to random mutagenesis, expressing the mutated DNA sequence, and screening for a mutant maltogenic amylase which shows higher thermostability, classified in class 435, subclass 441.

II. Claims 3 and 4, drawn to a method of producing a maltogenic amylase variant comprising modeling a parent alpha amylase on the three-dimensional structure of SEQ ID NO: 1; modifying the DNA encoding the parent alpha amylase to encode a mutant amylase having one or more amino acids deleted, inserted, or substituted; expressing and screening for a mutant alpha amylase having enzyme activity and at least one altered property relative to the parent, classified in class 435, subclass 69.1.

III. Claim 5, drawn to a method of constructing a variant of a parent maltogenic alpha-amylase comprising identifying an amino acid residue which is within 15Å from an active site residue of the parent amylase; substituting said amino acid residue with another amino acid residue which changes the electrostatic and/or hydrophobic surroundings of an active site residue, preparing the variant; and selecting a variant having an altered pH dependent activity as compared to the parent amylase, classified in class 435, subclass 69.1.

IV. Claims 6 and 7, drawn to a method of constructing a variant of a parent maltogenic alpha-amylase comprising identifying an internal cavity or crevice in the three-dimensional structure of the parent amylase; substituting an amino acid residue in the neighborhood of the cavity or crevice with another amino acid residue which increases the hydrophobic interaction and/or fills out or reduces the size of the cavity or crevice; preparing the variant; and selecting a variant having an increased thermostability as compared to the parent amylase, classified in class 435, subclass 69.1.

V. Claim 8, drawn to a method of constructing a variant of a parent maltogenic alpha-amylase comprising identifying an amino acid residue which is within 10Å

from a calcium binding site in the three dimensional structure of the parent amylase; substituting the amino acid residue with another amino acid residue so as to improve the interaction with the calcium ion; preparing the variant; and selecting a variant having increased thermostability as compared to the parent amylase, classified in class 435, subclass 69.1.

VI. Claim 9, drawn to a method of constructing a variant of a parent maltogenic alpha-amylase comprising identifying the substrate binding area in a model of the three dimensional structure of the parent amylase; modifying the substrate binding area by an amino acid substitution, deletion, or insertion; preparing the variant; and selecting a variant having an altered substrate-cleavage pattern as compared to the parent amylase, classified in class 435, subclass 69.1.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I-VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The processes of Groups I-VI are distinct both physically and functionally; require different process steps, reagents, and parameters; have different purposes; and produce different products.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

3. During a telephone conversation with Elias J. Lambiris on July 6, 2001, a provisional election was made with traverse to prosecute the invention of Group III, claim 5. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-4 and 6-9 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is directed toward a method using all possible three-dimensional crystal structures of any alpha-amylase. The specification, however, only provides a single representative species encompassed by the claim: an alpha-amylase having the three-dimensional structure of SEQ ID NO:2 depicted in the Appendix (pages 49-126). There is no disclosure regarding any other three-dimensional crystal structure of any alpha-amylase or crystallization conditions to use for any alpha-amylase in order to obtain its three-dimensional crystal structure. The specification also fails to describe additional representative species by any identifying structural characteristics or properties for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

7. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of constructing a variant of an alpha-amylase using the three-dimensional crystal structure of SEQ ID NO:2 depicted in the Appendix (pages. 49-126), does not reasonably provide enablement for a method of constructing a variant of any alpha-amylase using any three-dimensional crystal structure of any alpha-amylase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a method of constructing a variant of any alpha-amylase using any three-dimensional crystal structure of any alpha-amylase from any biological source, wherein said three-dimensional crystal structure is obtained using any crystallization method. The specification provides guidance and examples in making an alpha-amylase having the three-dimensional structure of SEQ ID NO:2 depicted in the Appendix (pages. 49-126). While molecular biological techniques and several crystallization methods for proteins are known in the prior art and the skill of the artisan are well developed, knowledge regarding a how to obtain a suitable crystal of any alpha-amylase for structure determination by X-ray in order to obtain the three-dimensional crystal structure of said alpha-amylase is lacking.

Thus, searching for suitable crystallization conditions for any alpha-amylase in order to obtain an adequate crystal for structure determination by x-ray diffraction method is well outside the realm of routine experimentation and predictability in the art of success is extremely low, see Branden et al. page 271. The amount of experimentation to identify conditions to grow a single crystal suitable for structure determination is enormous as taught by Branden et al. which encompasses many crystallization experiments for screening different parameters, such as pH temperature, protein concentration, and the nature of the solvent, in order to obtain a combination of parameters that may provide a crystals suitable for x-ray diffraction.

Since routine experimentation in the art does not include screening for protein crystallization conditions for any alpha-amylase where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the exact protein to be crystallized and the conditions under which any alpha-amylase would crystallize, and produce adequate crystal for structural determination by X-ray. Without such a guidance, the experimentation left to those skilled in the art is undue.

Claim Rejections - 35 U.S.C. § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Svendsen et al. Svendsen et al. teach the claimed method for constructing a variant of a parent alpha-amylase using the three-dimensional structure of said parent Termamyl-like α-amylase (see Appendix 1)

to make a variant having an altered property including an altered pH dependent activity (see entire publication and claims 1-14). Thus, the reference teachings anticipate the claimed invention.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L. Fronda whose telephone number is (703)305-1252. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703)308-3804. The fax phone number for this Group is (703)308-0294. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703)308-0196.

CLF

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